

Cite this: *Chem. Sci.*, 2022, **13**, 11246

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Synthesis of carboxamine *via* α -C(sp³)-H 2-pyridylation of O, S or N-containing compounds enabled by non-D-A-type super organoreductants and sulfoxide- or sulfide HAT reagents[†]

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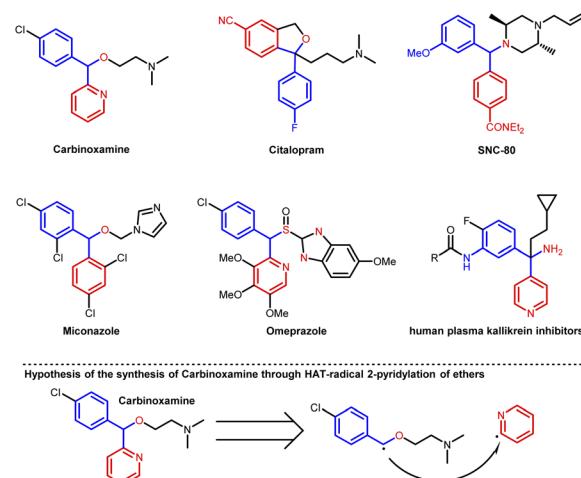
The radical cations of tertiary amines (R_3N) have been well-established as the precursors of HAT reagents in photochemical transformations. Similarly, thiols and thioacids bearing SH groups have also been widely applied as HAT reagents. Despite the fact that sulfoxides (R_2SO) and sulfides (RSR) also bear lone pairs of electrons, these compounds have been barely reported as HAT reagents in photocatalysis. On the other hand, the α -C-H 4-pyridylation of O or N-containing compounds has been documented, whereas 2-pyridylation remains challenging. However, the antihistamine and anticholinergic agent carboxamine is an ether bearing 2-pyridyl, which has not been obtained by the existing α -photoarylation of ether. In this work, we report the discovery of a non-donor-acceptor (D-A) type organic photoreductant CBZ6 and sulfoxide/sulfide synergistically catalyzed general α -C(sp³)-H arylation of ethers, thioethers and amines. By using as low as 1 mol% of CBZ6 as a recyclable organic photoreductant and sulfoxides or sulfides as a new type of HAT reagent, the 2- or 4-pyridylation of O, N, or S-containing compounds has been accomplished. This is the first base-free version of α -C-H 2-/4-pyridylation of O, N, or S-containing compounds. It is the first example of sulfoxides or sulfides working as HAT reagents. It is also the first general method for photocatalytic HAT 2-pyridylation of various ethers, amines or thioethers.

Received 23rd June 2022
Accepted 1st September 2022DOI: 10.1039/d2sc03504a
rsc.li/chemical-science

Introduction

Numerous diarylmethylalkyl ethers, sulfoxides and amines are pharmaceutical or bioactive molecules (Fig. 1). These compounds can be synthesized by the arylation of corresponding ether or amine precursors. For example, carboxamine is an antihistamine and anticholinergic agent, which might be prepared by the α -C-H 2-pyridylation of the corresponding ether (Fig. 1, bottom). The photocatalytic hydrogen atom transfer (HAT) is a straightforward route for α -C(sp³)-H functionalization of ethers, thioethers and amines.¹⁻⁵ Compared to the alternative two-step SET-deprotonation pathway under photochemical conditions in the presence of bases,⁴⁻¹¹ the HAT pathway^{3,12} does not need bases for deprotonation. Due to the mechanistic discrepancy, the regioselectivities of HAT and SET are usually quite different. For example, the C-H arylation of amines *via* the SET-

deprotonation process normally favors cyclic amines on the non-benzylic positions.⁴⁻¹⁰ In contrast, the HAT process can accomplish the benzylic C-H arylation of amines.^{11,12} Despite the fact that a photochemical HAT process exhibits unique regioselectivity as well as catalytic efficiency, fewer examples for



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[†] Electronic supplementary information (ESI) available. CCDC 2131995 and 2131996. For ESI and crystallographic data in CIF or other electronic format see <https://doi.org/10.1039/d2sc03504a>



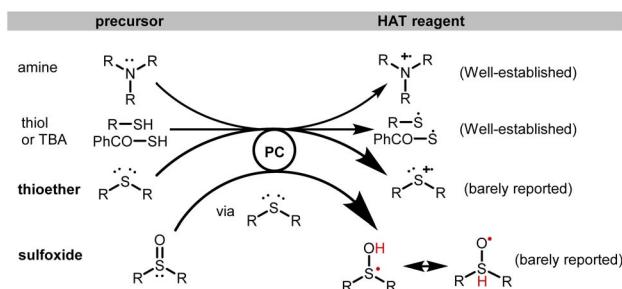


Fig. 2 The discovery of sulfoxides or sulfides as HAT-reagents.

the HAT C(sp³)-H arylation have been documented.¹² Nevertheless, the photo-arylation of ethers only goes through the HAT process rather than the SET-deprotonation process, which has been less reported than that of amines. In addition, with respect to a general problem in the α -C-H arylation of ethers or amines, 4-pyridylation has been frequently reported, whereas 2-pyridylation has been barely reported.^{13,14} However, the synthesis of carbinoxamine through the radical coupling between ethers and 2-pyridyl needs such 2-pyridylation (Fig. 1, bottom).

On the other hand, the radical cations of tertiary amines (R₃N) have been widely applied as HAT reagents in the photochemical redox transformations. Similarly, thiols and thioacids bearing SH groups have also been applied as HAT reagents.¹⁵ Despite the fact that sulfoxides (R₂SO) and thioethers (RSR) also

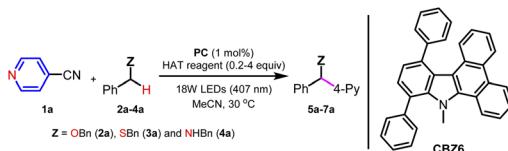
bear lone pairs of electrons, these S-containing compounds have been barely reported as HAT reagents in photocatalysis (Fig. 2). In this work, we report our discovery of sulfoxides or sulfides as HAT reagents and an organic photoreductant CBZ6 synergistically catalyzed α -C(sp³)-H arylation of ethers, thioethers and amines. Both 2- and 4-pyridylation of O, N, or S-containing compounds has been accomplished.

Results and discussion

Photocatalysts (PCs) and HAT reagents were screened in α -C(sp³)-H 4-pyridylation of **1a** with ether (**2a**), thioether (**3a**) and amine (**4a**) (Table 1). First, dibenzyl sulfoxide **8a** was applied to investigate whether sulfoxide can act as a HAT reagent. It was found that **8a** is efficient to afford α -pyridylation products **5a**, **6a** and **7a** in 81%, 85%, and 82% yields, respectively (Table 1, entries 1–3). The same reaction conditions work for either ethers, thioethers or amines, suggesting the HAT pathway rather than the SET-deprotonation way because it is difficult for ethers to follow the SET pathway. Even the solvent DMSO was reactive without extra sulfoxides, and 98% **7a** was obtained (entry 5). The reaction in the absence of sulfoxide **8a** gives no conversion of starting materials (entry 4), indicating that the HAT reagent is necessary for this reaction. In comparison, several common PCs were screened, and no better results were achieved (entries 6–10).

Next, several potential HAT reagents were examined with a loading of 20 mol%. The tertiary amine DABCO is reactive but

Table 1 Reaction conditions



Entry	PC	HAT reagent	Yield (%)
1 ^a	CBZ6	Ph ₂ S=O (8a)	5a, 81
2 ^a	CBZ6	Ph ₂ S=O (8a)	6a, 85
3 ^a	CBZ6	Ph ₂ S=O (8a)	7a, 82
4	CBZ6	None	7a, 0
5	CBZ6	DMSO (no MeCN)	7a, 98
6	Eosin Y	DMSO (no MeCN)	7a, trace
7	Rhodamine B	DMSO (no MeCN)	7a, trace
8	Thioxanthen-9-one	DMSO (no MeCN)	7a, 25
9	Ir(ppy) ₃	DMSO (no MeCN)	7a, 40
10	TBADT	DMSO (no MeCN)	7a, 0
11	None	DMSO (no MeCN)	7a, 0
12 ^b	CBZ6	DABCO	7a, 22
13 ^b	CBZ6	1-Dodecanethiol (9a)	7a, 55
14 ^b	CBZ6	iPr ₃ SiSH (9b)	7a, 23
15 ^b	CBZ6	4-ClC ₆ H ₅ SH (9c)	7a, 76
16 ^b	CBZ6	PhSPh (10)	7a, 42
17 ^b	CBZ6	(4-ClC ₆ H ₅) ₂ S=O (8b)	7a, 76
18	PhC(O)SH (TBA)	K ₃ PO ₄ in DMA (455 nm, ref. 12)	7a, 63
19	Ir(ppy) ₃	9a, 9c or 10	7a, 0
20	Ir(ppy) ₃	4'-BuC ₆ H ₄ SH (9d) (425 nm, ref. 11)	7a, trace

^a 4 equiv. Ph₂SO. ^b 20 mol% of HAT reagents.

gives a low yield (entry 12). Thiols such as 1-dodecanethiol and iPr_3SiSH are also reactive to give moderate yields even in the absence of bases (entries 13 and 14). Thiophenol 4-Cl-PhSH is a better HAT reagent than 1-dodecanethiol (entry 15 vs. 13). Surprisingly, diphenyl thioether **10** is also reactive as a HAT reagent (entry 16). Sulfoxide **8b** is an even better HAT reagent than thioether **10**, and 76% yield was obtained (entry 17). Thienobenzoic acid (TBA)-catalysis, which demonstrated good catalytic activity in the 4-pyridylation of amines,¹² gave decreased yield (entry 18). In addition, the 4-pyridylation of dibenzyl amine **4a** failed when using $Ir(ppy)_3$ as a PC (entries 19 and 20). Finally, diphenyl sulfoxide **8a** was chosen as the HAT agent under the standard reaction conditions. **CBZ6** (1–5 mol%) was utilized as an organic photoreductant. Acetyl nitrile was the optimized solvent.

After the standard reaction conditions have been established, the scope of ethers, thioethers and amines was investigated. First, O-containing compounds including ethers and alcohols were subjected to the standard reaction conditions. What should be pointed out is that ethers are challenging substrates for photocatalytic α -C–H arylation *via* the SET pathway. The HAT pathway is a straightforward pathway for ethers. Nevertheless, only one example of α -C–H 4-pyridylation of dibenzyl ether with moderate yield (42% yield) was demonstrated in a previous study¹² with noble metal PCs, whereas no example for 2-pyridylation has been documented.^{3,11,12} With respect to the alcohols, neither 2-pyridylation nor 4-pyridylation has been reported. Although the silyl-protected alcohols are suitable for 4-pyridylation, no example of 2-pyridylation has been documented. Therefore, the photocatalytic synthesis of carbinoxamine *via* the photocatalytic α -C–H 2-pyridylation has not been accomplished to date. To our delight, not only 4-pyridylation but also 2-pyridylation was achieved by the photocatalysis of **CBZ6** with Ph_2SO as the HAT reagent (Fig. 3). Both dibenzyl ethers (**5a**, **5b**) and benzyl methyl/tert-butyl ethers (**5c**, **5d**) afford good yields. Cyclic ethers (**5e**, **5f**) gave comparable yields. The increase of steric hindrance leads to the decrease of yield to 62% (**5g**). The arylation of silyl ether (**5h**) and benzyl alcohol (**5i**) affords the desired products in 83% and 77% yields, respectively. The α -C–H 2-pyridylation has been barely reported for ethers. It was found that this **CBZ6**-sulfoxide system is a powerful tool for 2-pyridylation. The 2-pyridylation of ether was achieved in moderate to good yields (**5j**–**l**).

The α -C–H arylation of thioethers is normally achieved by Pummerer rearrangement.¹⁶ Fortunately, the 4-pyridylation of methyl benzyl ether or dibenzyl thioethers was achieved with 75–85% yields (**6a**–**c**) (Fig. 3). The α -C–H 2-pyridylation of thioethers was also successfully realized in the presence of the **CBZ6**-sulfoxide system providing 2-pyridylation products **6d**–**g** in moderate yields.

The success of 2-pyridylation of ethers encouraged us to pursue the synthesis of carbinoxamine from a simple ether. A 3-step synthesis of carbinoxamine was accomplished with a total 44% yield *via* a key gram-scale 2-pyridylation of protected benzyl alcohol (Fig. 3, bottom).

Compared to ethers or thioethers, amines are more reactive and might follow either the SET or HAT pathway for the α -

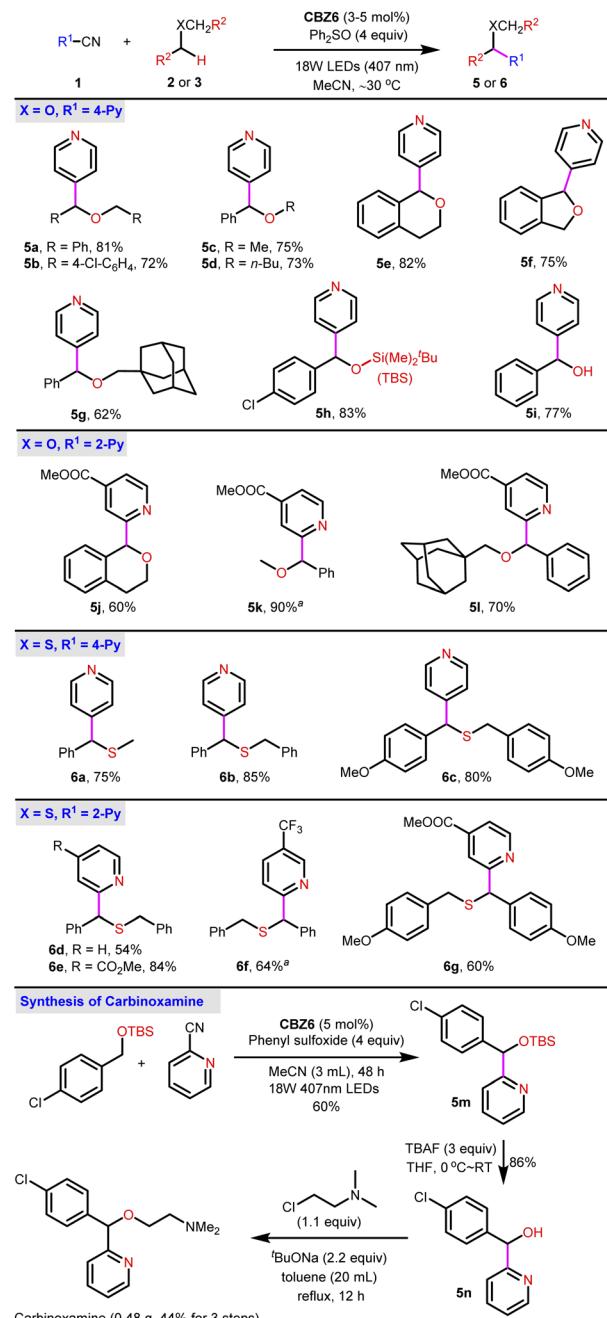


Fig. 3 Arylation of ethers, alcohols, and thioethers with 2-cyano or 4-cyanopyridines and the application in the total synthesis of carbinoxamine. **5i** was obtained with 0.5 equiv. 1-dodecanethiol instead of Ph_2SO .

arylation reactions under the irradiation of visible light. In previous reports, cyclic amines were widely examined in the photocatalytic 4-pyridylation *via* the SET-deprotonation pathway where bases were necessary for deprotonation. The arylation of acyclic amines has been less reported and was mainly concentrated on the non-benzylic positions. Thienobenzoic acid (TBA)-catalysis is the corner stone for the HAT arylation of amines.¹² However, the 2-pyridylation of dibenzyl amine **4a** fails without either $Ir(ppy)_3$ or TBA PCs (Fig. 4, bottom, conditions A and B). Nevertheless, despite the fact that 4-



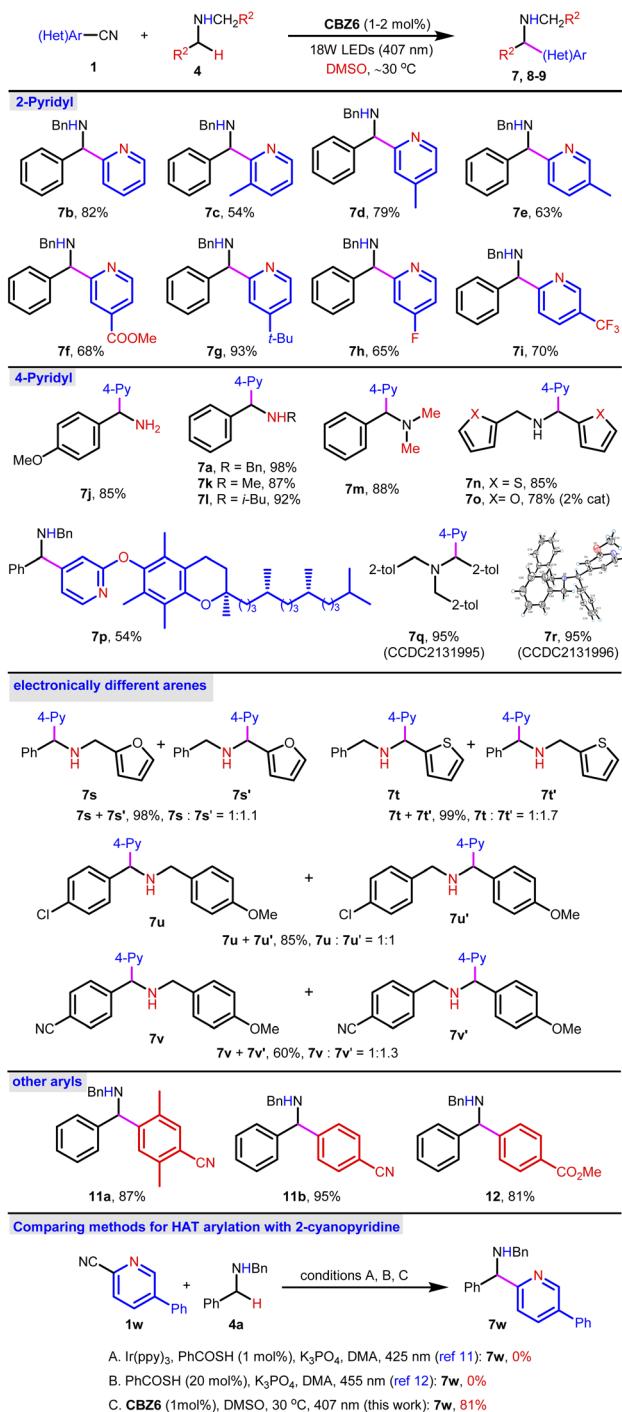


Fig. 4 Arylation of amines with 2-cyano or 4-cyanopyridines.

pyridylation has been well established, the 2-pyridylation of either ethers or amines remains challenging. To test the catalytic ability of the **CBZ6**-sulfoxide system in 2-pyridylation, dibenzyl amine **4a** was subjected to the standard reaction conditions using DMSO as a solvent and HAT reagent (Fig. 4, top). Product **7b** was isolated in 82% yield. A range of nitriles were applied as 2-pyridylation reagents, and the desired products **7c–i** were obtained in up to 93% yields. Besides the 2-pyridylation, the 4-pyridylation of amines was also smooth. The

primary amine (**7j**), secondary amines (**7a, k–l**), and tertiary amine (**7m**) were all successful. The amines bearing heterocyclics (**7n–o**) as well as the arylation reagent bearing a 2-substituent (**7p–r**) were investigated, and the corresponding products were achieved in 53–95% yields. When amines bearing two electronically different arenes (**7s–v**) were used, a mixture of diastereomers was obtained in moderate to excellent yields. Other typical aryls were also examined (**11a–b, 12**) giving the desired products in good to excellent yields. All the above-mentioned examples indicate that the **CBZ6**-sulfoxide system is a general and efficient catalytic system for the α -C–H arylation of O, S, and N-containing compounds.

With respect to the reaction mechanism, the key point is the catalytic model of **CBZ6** and the role of sulfoxides. Is it a SET or HAT process? The control experiments have been carried out to reveal the nature of this catalytic system. A mixture of Ph_2NMe and Bn_2O was treated under standard reaction conditions for 8 hours, and only 25% **5a** was obtained (Fig. 5a). It is obvious that dibenzyl ether is more reactive than diphenyl methyl amine. Supposing ether can only follow the HAT pathway whereas amine can follow either the SET or HAT pathway, the above results support the HAT pathway.

The kinetic study shows a first-order dependence of the initial rate on the concentration of Ph_2SO , indicating that sulfoxides directly participate in the rate determining step (Fig. 5b). The KIEs of 2.5 for **4p** and 3.1 for **4q** are consistent with the rate determining step of H-atom abstraction (Fig. 5c). The effect of sulfoxides was then investigated, and the results summarized in Fig. 5d indicate that sulfoxide works as a H-abstractor. The HRMS experiments detected intermediates **13** and **15**, suggesting the existence of intermediates **14** and **16** (Fig. 5e). Thioether PhSPh proved to be generated from the decomposition of sulfoxide (Fig. 5f). When PhSPh was used as the HAT reagent, the arylation of **4a** with **1a** was achieved in 42%. Simultaneously, PhSPh disappeared and has been converted to Ph_2SO . All the aforementioned evidence can prove that intermediate **16** is the catalytically active species for the HAT reagent in this arylation. Note that the reaction initialized from either thioesters or sulfoxides; the key intermediates as HAT reagents should be the same, probably radical **16**.

Fluorescence quenching experiments of **CBZ6** illustrate the quenching effect with 4-cyanopyridine **1a** (Fig. 6a). The Stern–Volmer plot shows that the excited state of **CBZ6** has been quenched by **1a**, and the quenching effect increased with the growth of the concentration of **1a** (Fig. 6b). Although the quenching effect between 4-cyanopyridine and Bn_2NH was detected at 307 nm, no quenching was observed in the range of around 407 nm (Fig. 6c and d), indicating that the EDA between **1a** and **4a** is not possible at 407 nm, therefore the SET model can be ruled out in this work. The on–off experiments prove the necessity of light.

Based on the experimental evidence demonstrated in Fig. 5 and 6, a proposed reaction mechanism is illustrated in Fig. 7. **CBZ6** works as a redox neutral PC, and sulfoxides act as the HAT reagents. **CBZ6** has been established as a powerful organic photoreductant (Fig. 6f).^{17,18} Thioether **i** is generated via the decomposition of sulfoxide under the irradiation of a LED at



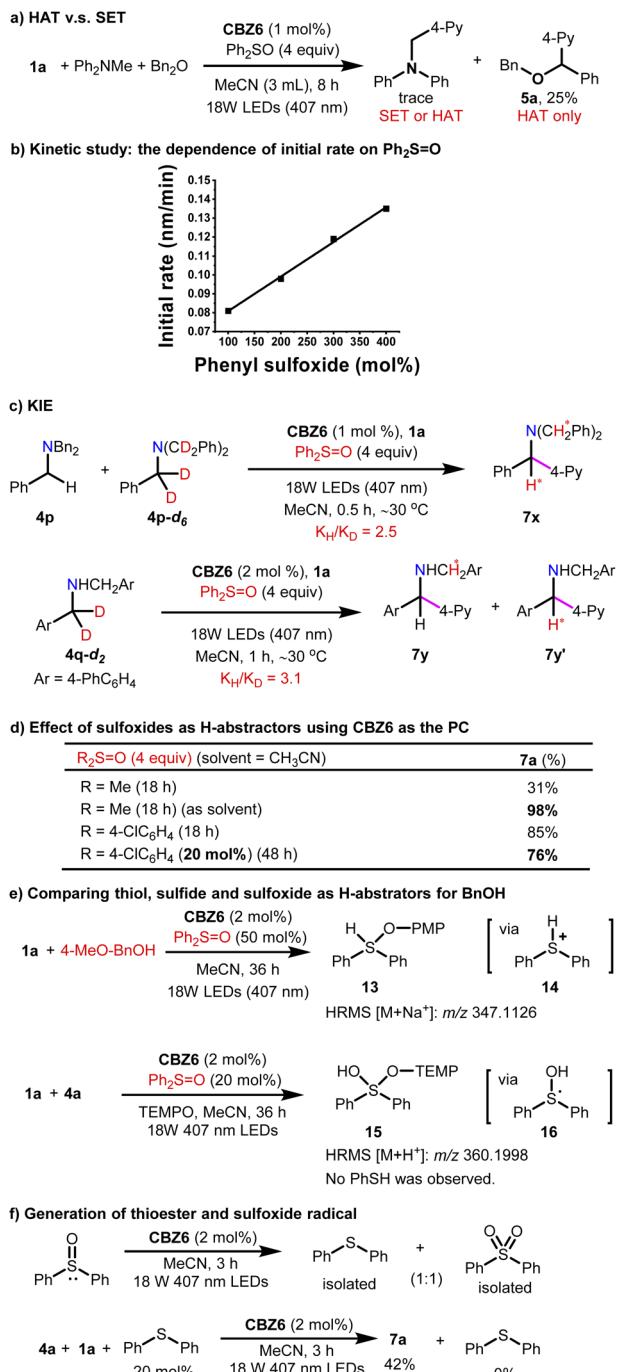


Fig. 5. Control experiments

407 nm. This thioether is oxidized to thioether radical cation **ii** by the CBZ6 radical cation which comes from the quenching effect with nitrile **1**. Intermediate **ii** can abstract the α -H-atom of ethers or amines to form **iii**, which can be detected (Fig. 5e). It can also transform into radical **iv**, followed by the isomerization to O-centered radical **v**. Radical **iv** can be detected by a spin trapping reagent TEMPO with HRMS-ESI ($M + H^+$ 360.1998). What should be noted is that PhSH has not been detected or isolated, suggesting that PhSH cannot be the reactive HAT reagent in this work. O-radical **v** abstracts the H atom of ethers

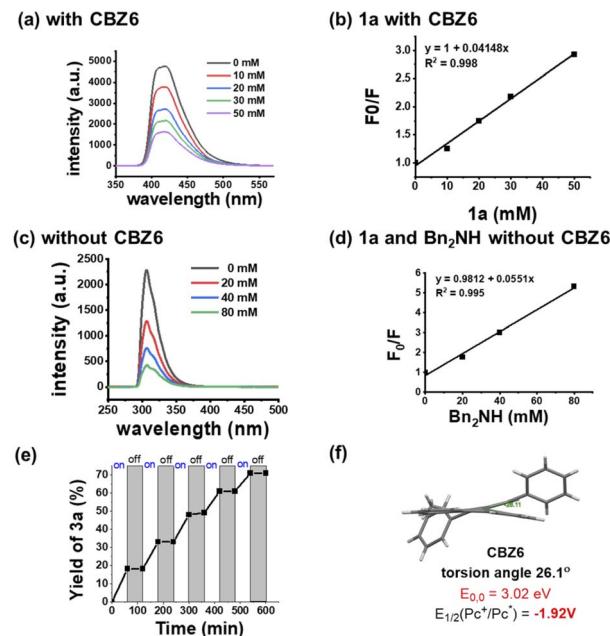


Fig. 6 Control experiments: the (a) fluorescence quenching effect between **1a** and **CBZ6**, (b) Stern–Volmer plot (**1a** vs. **CBZ6**), (c) fluorescence quenching effect between **1a** and **4a** (note: no effect above 400 nm), (d) Stern–Volmer plot (**1a** vs. **4a**), (e) on–off control, and (f) the molecular structure of **CBZ6**

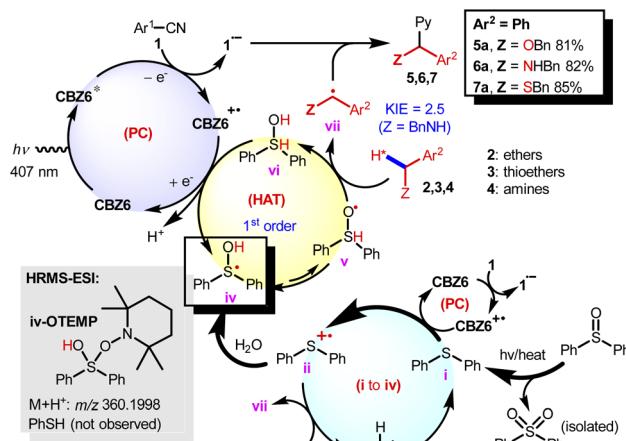


Fig. 7 Proposed mechanism

or amines to yield α -C-radical **vii**, followed by the addition to a nitrile radical to afford target α -C-H arylation products 5–7. Intermediate **vi** is oxidized to regenerate **iv** by the **CBZ6** radical cation. Because neither thiol nor thioether is observed in the reaction, the catalytically active species of the HAT reagent is assigned to radical **iv** or **v**. Radical **iv** is too bulky to abstract the H atom; **v** is believed to be the reactive form.

Conclusions

In conclusion, we develop a general visible light organic photocatalytic α -C(sp³)-H arylation of ethers, thioethers and

amines by using as low as 1 mol% of **CBZ6** as a recyclable organic photoreductant and sulfoxides and thioethers as unique hydrogen abstractors. The first base-free photocatalytic α -C–H arylation of O, S and N-containing compounds is thus presented. Sulfoxides and thioethers have been first discovered as HAT reagents. 2-Pyridylation of ethers and amines is therefore enabled by the **CBZ6**-sulfoxide HAT system. Consequently, the antihistamine and anticholinergic agent carbinoxamine was synthesized by this method in total 44% yield on the gram scale. The insight into the mechanism as well as further applications of this method are being studied in our laboratory.

Data availability

All experimental data and detailed experimental procedures are available in the ESI.†

Author contributions

X.-C. C., H. Z. and Y.-P. W. performed experiments and characterization. X.-C. C., Y.-B. K. and J.-P. Q. conceived the research plan. Y.-B. K. and J.-P. Q. supervised the project, wrote the manuscript and secured funding.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Key R&D Program of China (No. 2021YFA1500100), the National Natural Science Foundation of China (22271268, 21922109, 21672196, and 21831007), the National Synchrotron Radiation Lab of the University of Science and Technology of China (UN2018LHJJ), and the Start-up Funding from Nanjing Tech University (39837134) for financial support.

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